

# Measurement and Management of Health-Related Quality of Life in Lung Cancer

**Kimberly Davis, PhD, Susan Yount, PhD, Lynne Wagner, PhD, and David Cella, PhD**

Dr. Davis is Assistant Professor at the Georgetown University Medical Center in Washington, DC. Dr. Yount and Dr. Wagner are Assistant Professors and Dr. Cella is Professor at Northwestern University Medical School in Evanston, IL. Dr. Yount is also Director of Research Operations at the Center on Outcomes, Research and Education, where Dr. Wagner is Clinical Research Scientist and Dr. Cella is Director.

Address correspondence to: Kimberly Davis, PhD, Georgetown University Medical Center, LCCC-Cancer Control Program, Department of Oncology, 2233 Wisconsin Ave. NW, Suite 317, Washington, D.C. 20007; E-mail: nuage712000@yahoo.com.

## Abstract

The 5-year survival rate for lung cancer has been and remains very low, and patient experience is characterized by a heavy symptom burden leading to poorer health-related quality of life (HRQL). In light of these facts, treatment remains primarily palliative with a focus on improving quality of life, particularly through symptom management. Increasingly, clinical research has evaluated both traditional clinical endpoints as well as quality of life as primary outcome variables. This is due in part to recent data in which patient-reported health data have been found to have prognostic value in lung cancer. This paper reviews the literature to date about lung cancer survivors, HRQL conclusions from recent clinical trials, and several barriers to the incorporation of HRQL information into daily clinical practice. Finally, we describe some recent clinical applications of the integration of HRQL information into routine clinical practice with advanced lung cancer patients.

## Introduction

Lung cancer is the most common cancer worldwide,<sup>1</sup> the second most common cancer in the United States,<sup>2</sup> and the leading cause of cancer death.<sup>3</sup> The 5-year survival rate for patients diagnosed with lung cancer in 2003 is projected to be 15%, which is only 1–2% better than the survival rate over the past 4 years.<sup>4,5</sup> Survival for those with early stage or limited disease approaches a more favorable 50%.<sup>6</sup> The majority (approximately 75%) of all lung cancer is classified histologically as non–small-cell cancer (NSCLC), with the remaining 25% being small-cell lung cancer (SCLC).<sup>7–8</sup> Most lung cancers are undetected until symptoms develop and patients present with locally advanced or metastatic disease. Patients with advanced disease face a shortened life expectancy that is increasingly symptomatic, often due to disease progression. As cure is not an option for advanced disease, the goal of treatment is focused on maintenance of function and symptom palliation while minimizing toxicity.

While survival, tumor response, and time to disease progression have been traditionally viewed as the most critical endpoints in clinical trials of cancer treatment, patient-reported outcomes such as health-related quality of life (HRQL) and symptom experience have been increasingly accepted as equally important.<sup>9</sup> This is particularly true for people with advanced lung cancer, where treatment tends to be focused primarily on palliative versus curative intent.<sup>6,10–13</sup> The impact of advanced lung cancer on patients' HRQL and symptom experience is significant and well documented. Patients typically experience disruptions in their capacity to engage in physical activities, and this has been associated with poorer psychological well-being.<sup>14–16</sup> Comorbid conditions, such as pulmonary and cardiovascular disease, are common because of the relationship of lung cancer to smoking, and these conditions also contribute to functional decline. Psychological distress is also linked with the significant symptomatology associated with lung cancer (eg, pain, dyspnea, fatigue, functional decline, anorexia, sleep disturbance). Symptoms may be relieved with treatment, but some are refractory to medical intervention. Further, most patients experience multiple simultaneous symptoms, which contributes further to declines in HRQL.

The patient's stage of disease and, by extension, prospect for curative therapy, carries important implications for patient-reported outcomes, including HRQL. In the adjuvant setting, HRQL outcomes are not likely to improve in the short-term and may, in fact, worsen. This is because the disease

## Keywords

Lung cancer, symptom management, quality of life, clinical applications

itself rarely produces significant symptoms in the early stages, and adjuvant therapies can cause symptomatic toxicity. One exception to this is mood, which tends to improve after patients begin a new therapy. The value of curative therapy tends to be based on more distal outcomes such as lengthened survival probability. In contrast, HRQL is often a more primary concern when evaluating treatment for advanced disease, where cure is no longer a realistic option. When people are receiving treatments for advanced disease, they may experience improvement in their symptom and HRQL status in the short term, especially with less toxic therapies.

There are now a number of validated measures available for screening for disease- and treatment-related changes in symptoms and HRQL. These measures have gained wide acceptance in clinical trials, but their use in clinical practice is very limited. A number of barriers preclude the routine collection and use of HRQL data in clinical practice. However, several recent pilot studies have demonstrated feasibility, acceptability, and clinical utility of collection and integration of HRQL data in clinical practice in patients with advanced lung cancer. The use of computer technology for reducing patient and administrative burden in assessment and presentation of HRQL data in real-time is currently under development in clinical and research applications.

This article will briefly review the limited literature on lung cancer survivors, summarize the HRQL findings of recent clinical trials of patients with advanced lung cancer and the methodological issues that limit the ability to draw HRQL conclusions from these trials, address barriers to the integration of HRQL information in clinical practice, and describe 2 novel clinical applications of how HRQL and symptom information are currently being used in clinical practice.

## Lung Cancer Survivors

While the 5-year survival rate for patients diagnosed with lung cancer has remained consistently low, the rate for those with limited or early stage disease has remained closer to 50%.<sup>6</sup> For patients with NSCLC, surgery offers the best chance for cure, yet only 20% of these patients have operable cancer. Overall 5-year survival rates are 55% for patients with stage I disease and 25% for stage II disease.<sup>17</sup> Patients with completely resected tumors without mediastinal node involvement have a slightly better outlook, with 5-year survival of approximately 40%.<sup>18</sup>

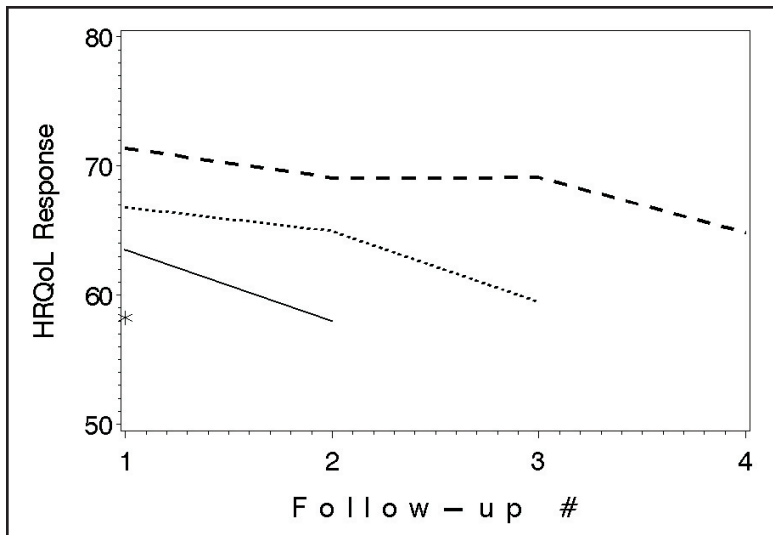
Randomized clinical trials (RCTs) of postoperative adjuvant chemotherapy have been shown to prolong survival, particularly with cisplatin-based regimens.<sup>19-21</sup> While a meta-analysis of 8 RCTs demonstrated a 13% reduction in the risk of death corresponding to a 5% absolute survival benefit at 5 years,<sup>22</sup> further clinical benefit of postoperative chemotherapy was unclear in the mid to late 1990s, given the therapeutic agents available at that time.

At the present time, preoperative chemotherapy is being given for patients with NSCLC with stage IIIA disease. Results from several nonrandomized studies have demonstrated response rates between 50% and 75%, with subsequent re-

sectable rates of 65–90% and 3–5-year survival rates of 17–40%.<sup>23-28</sup> While these results are promising, the data must be interpreted with caution for several reasons. First, there is a significant amount of heterogeneity in the eligibility criteria across each of the cited studies. Second, none of these studies was a randomized trial. However, results from 2 subsequent small randomized studies comparing surgery with and without preoperative chemotherapy demonstrated positive benefits of chemotherapy for patients with stage IIIA disease.<sup>29-30</sup> Additionally, results from a small randomized pilot study of patients with early stage (IB, II, and IIIA) resectable NCSLC also demonstrated the positive benefit of preoperative chemotherapy.<sup>31</sup> Preoperative chemotherapy was well tolerated and resulted in improved symptom status prior to surgery, with some patients also experiencing improved performance status.<sup>31</sup> While these results are compelling, a significant limitation of all of these studies, randomized and nonrandomized, is the small sample size. Large multicenter phase III RCTs are, therefore, necessary to confirm these findings.

The long-term survival outlook for patients with SCLC has been considerably less well studied and is, therefore, less well understood. While SCLC tends to be very chemosensitive, with response rates of 80–90%,<sup>32-33</sup> most patients experience disease progression after treatment is discontinued and need second-line treatment. Long-term survival for patients with extensive disease remains mostly anecdotal, and given that the 5-year survival for those with limited disease is  $\leq 5\%$ , information about survival is severely lacking. In one study of long-term survivors (beyond 30 months) with SCLC, 3 major findings included: (1) the side effects of treatment were relatively mild, allowing 40% of patients to return to work within 2 years of diagnosis; (2) those who relapsed benefited from second-line treatment; and (3) 5- and 10-year survival is attainable, with rates of 68% and 44%, respectively.

For patients with SCLC, there are a number of different treatments that have less toxic effects with respect to symptoms and HRQL, including newer chemotherapeutic agents and cranial irradiation. Gemcitabine (Gemzar, Lilly), one of these newer agents, continues to demonstrate improved tolerability and the synergistic interaction between gemcitabine and platinum agents appears to be less toxic, yet equally effective for patients with extensive SCLC.<sup>35</sup> Cranial irradiation is often given to the large percentage of patients with SCLC who develop brain metastases. In a recent review, authors set out to develop evidence-based practical guidelines for prophylactic cranial irradiation in patients with SCLC. In 4 of 6 RCTs and 1 individual meta-analysis, patients who achieved a complete response after induction therapy showed evidence of a disease-free survival benefit, and in the meta-analysis there was an overall survival benefit.<sup>36</sup> While there appears to be insufficient evidence to make any definitive recommendations with respect to dose, there is evidence from trials with data for up to 2 years of follow-up that prophylactic cranial irradiation does not produce significant neurotoxicity. Additionally, evidence from another trial suggests that prophylactic cranial irradiation does not negatively affect HRQL in



**Figure 1.** Average FACT-Lung TOI scores stratified by time of dropout.

HRQoL=health-related quality of life, FACT=Functional Assessment of Cancer Therapy, TOI=Trials Outcome Index.

Reprinted with permission from Fairclough DL.<sup>40</sup>

the first 12 months following therapy. There was insufficient evidence regarding the long-term HRQL effects. The limited available data about lung cancer survivors suggest that some patients experience stability or even benefit in HRQL as a result of treatment. Overall, however, lung cancer remains a disease with a relatively poor prognosis, with newer therapies providing modest survival advantages.

### HRQL in Advanced Lung Cancer

While interest in and incorporation of HRQL assessment into RCTs in advanced lung cancer has increased dramatically over the past 2 decades, the degree to which this has been successfully achieved is more limited. Because of the methodological limitations associated with HRQL data, especially missing data problems inherent in longitudinal measurement of HRQL, the HRQL findings reported in a number of RCTs must be interpreted with caution. Prior to summarizing the general HRQL findings in advanced lung cancer, some limitations of missing data will be discussed.

### Missing Data Issues in Longitudinal HRQL Data

Patients participating in clinical trials that include assessment of HRQL are typically asked to assess their HRQL prior to randomization (baseline) and at several times during the study period. However, patients fail to complete some or all assessments for a variety of reasons, and this creates the problem of missing data. The reasons for missing data can be administrative in nature (ie, the staff forgets to administer the questionnaire), or related to patient factors. Delays in treatment due to toxicity or other factors may result in assessments not being administered or being administered at time intervals outside those specified in the protocol. Qian et al<sup>37</sup> provided such an example from an RCT in SCLC, where the number of symptom assessment forms completed per patient ranged from 1 to 9, and the symptom forms were completed at 100 different time points versus the

12 specified in the protocol.<sup>37</sup> An observation all too common in lung cancer RCTs is that the most symptomatic patients tend to drop out of trials due to disease progression or death.<sup>38</sup> Patients with deteriorating health status are known to be less compliant with further HRQL evaluations.<sup>39</sup>

Missing data is one of the most significant issues in analyzing and interpreting HRQL results, regardless of whether the problem stems from poor patient compliance or data collection difficulties. The first potential problem with missing data is the loss of power to detect clinically meaningful differences in HRQL scores as a result of a reduced number of observations, especially in studies with small sample sizes.<sup>40</sup>

The second problem is the potential bias introduced as a result of missing data, especially when attrition due to symptomatology is directly related to HRQL as an

endpoint.<sup>38,40</sup> If analyses are based only on the observed data of patients with good HRQL because those with poor HRQL have dropped out of the trial, HRQL will be overestimated. While the reasons for patients dropping out or not completing assessments can be informative, most statistical analyses of HRQL data assume the missing data occur at random.<sup>41</sup> Exclusion of these data from the analyses may lead to several consequences, including overly discouraging interpretations of findings regarding potential treatment effects, and false conclusions regarding the benefits of treatment and/or change in HRQL over time.

Such nonrandom attrition, or “informative censoring,” affects the study’s external validity for generalization of results, and internal validity if there is differential attrition among comparison groups due to the treatment effect. Fairclough<sup>40</sup> illustrated the potential impact of nonrandomly missing HRQL data on interpretation of results by plotting HRQL scores of NSCLC patients (measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) Trial Outcome Index (TOI) who had been grouped by the time of their last HRQL assessment (ie, time of dropout). The TOI is a 21-item aggregate symptom index of the scores from the physical well-being (PWB), functional well-being (FWB), and lung cancer subscale (LCS) and is thought to be the most relevant and precise indicator of patient reported health specific to patients with lung cancer<sup>42</sup>. Figure 1 illustrates that patients who dropped out earlier had poorer TOI scores at baseline, and TOI scores had declined at the time of the assessment just prior to their dropout.

Further contributing to the difficulty of interpreting HRQL findings, few RCTs report patient dropout and the percent of missing HRQL data.<sup>43,44</sup> In a review of international RCTs published between 1989 and 2002, only 18 of 29 (62%) of trials adequately reported how much HRQL data was missing and how this was handled.<sup>43</sup> The problems associated with

missing data are increasingly recognized in the literature, and many investigators have proposed potential solutions or analytical strategies to address missing data problems.<sup>38,40,45-48</sup>

### Summary of HRQL Findings in Advanced Lung Cancer

Methodological issues associated with HRQL data collection and analysis aside, studies have shown that the HRQL of patients and their families with lung cancer is affected by patient-, treatment-, and disease-related factors. Chief among these is the constellation of symptoms at presentation and those that develop with disease progression and/or treatment. In one study of 673 patients with advanced NSCLC, presenting symptoms included dyspnea (87%), cough (86%), pain (81%), loss of appetite (75%), and hemoptysis (41%), with 81% of patients presenting with 3 or more symptoms.<sup>49</sup> Presenting symptoms related to paraneoplastic syndromes are also common such as weight loss (46%), anorexia (24%), and weakness (33%).<sup>50</sup> These symptoms impair patients' ability to work or maintain activities of daily living.

The impact of chemotherapy on survival and HRQL in patients with NSCLC has been controversial for years. The addition of chemotherapy to best supportive care, primarily cisplatin-based regimens, has demonstrated a significant but modest impact on overall survival.<sup>22,51-53</sup> In addition, chemotherapy can reduce cancer-related symptoms and improve HRQL in patients with advanced NSCLC.<sup>43,54-61</sup> Further, the side effects of chemotherapy (eg, nausea/vomiting, constipation, hair loss, peripheral neuropathy), do not seem to impair patient ratings of overall HRQL. Despite the benefits to survival and HRQL of first-line, platinum-based combination chemotherapy regimens,<sup>62</sup> virtually all patients will experience disease progression, and these patients may be eligible for second-line treatment. The results of a range of second-line chemotherapy regimens have shown a beneficial impact on survival, HRQL, and disease-related symptoms.<sup>61,63-65</sup>

Treatment for SCLC has tended to be considerably less controversial than for NSCLC. Combination therapy, with or without radiation therapy, is generally the treatment of choice in SCLC.<sup>66</sup> Comparisons of intensive regimens versus standard therapy have produced mixed results. Some report a very modest survival advantage for intensive treatment without a sacrifice in HRQL.<sup>67</sup> Consistent with findings in NSCLC,<sup>57-58,67</sup> studies comparing chemotherapy versus best supportive care regimens have suggested that patients with SCLC receiving chemotherapy experience better tumor responses and improved HRQL (but more severe side effects) compared with patients receiving palliative treatment.<sup>68</sup> Other studies have suggested that less intensive treatments lead to better HRQL compared with more intensive treatment regimens or those with a greater number of treatment cycles.<sup>69-71</sup> In SCLC, central nervous system (CNS) involvement is common, often requiring cranial irradiation for as long as 6–12 months. Cranial irradiation can result in cognitive dysfunction and encephalopathy, which further contribute to the adverse impact of treatment for lung cancer on patients' HRQL.

### Relationship Between HRQL and Clinical Endpoints

Recent studies in lung cancer have yielded good quality HRQL data that allow us to examine the relationship between HRQL and traditional clinical endpoints, such as survival, tumor response, time to progression, as well as the prognostic value of HRQL data in patient survival. Novel targeted agents have been more recently introduced in the treatment of NSCLC and have been shown to possess the potential to improve both tumor response and HRQL.<sup>72</sup> One such targeted therapy is gefitinib (Iressa, AstraZeneca), a selective epidermal growth factor receptor tyrosine kinase inhibitor. The Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL)-1 and -2 trials were phase II, double-blind, randomized, dose-comparative studies of gefitinib at 250 mg/day or 500 mg/day for second-line, third-line or greater therapy in patients with advanced NSCLC.<sup>73-75</sup> The IDEAL-1 trial was conducted in Europe, Japan, South Africa, and Australia while IDEAL-2 was conducted in the United States with NSCLC patients who were symptomatic at baseline. Symptom improvement, as measured by the Lung Cancer Subscale (LCS) of the FACT-L, was observed in 43% of patients receiving 250 mg/day and 35% of patients receiving 500 mg/day.<sup>76</sup> Symptom improvement on the IDEAL trials occurred rapidly; the median time to symptom improvement was 8 days in IDEAL-1 and 10 days and 9 days in the 250- and 500-mg groups, respectively, in IDEAL-2. In IDEAL-1 and -2, improvement in symptoms was also associated with objective disease response and both overall and progression-free survival.<sup>73</sup> Improvements in HRQL, as measured by the FACT-L, were also demonstrated in these trials. The HRQL improvement rate was 23.9% and 21.9% for the 250- and 500-mg/day groups, respectively on IDEAL-1, and 34% and 23% for the 250-mg/day and 500-mg/day groups, respectively, in IDEAL-2.<sup>76</sup> For those patients whose HRQL had improved, 45.7% of those in the 250 mg/day group and 46.2% of those in the 500 mg/day group on IDEAL-2 were still showing improvement after 90 days of treatment.<sup>75</sup> IDEAL-1 produced comparable findings to those of IDEAL-2.<sup>73</sup>

Patient-reported health data such as HRQL have also been found to have prognostic value in lung cancer.<sup>77-80</sup> In the Eastern Cooperative Oncology Group (ECOG) study E5592, comparing cisplatin/etoposide versus cisplatin/paclitaxel in advanced NSCLC, baseline and follow-up patient-reported health data from the FACT-L were predictive of clinical outcomes after controlling for clinical factors.<sup>81</sup> Specifically, the baseline PWB and TOI aggregate index scores predicted response to treatment, disease progression, and survival. Additionally, change in PWB was predictive of response to treatment and survival, and change in TOI was predictive of time to progression.

Symptom experience and distress have also been associated with various clinical endpoints. Symptom distress, as measured by the Symptom Distress Scale,<sup>82</sup> was the most important predictor of survival in patients with advanced lung cancer after adjusting for age, functional status, and personality traits.<sup>83</sup> In addition, the LCS, a 7-item subscale of the FACT-L that measures lung cancer-specific symptoms and concerns, has been

shown to correlate with clinical parameters in advanced lung cancer. In ECOG E5592, patients with lower baseline LCS scores (ie, more symptoms) had lost 5% or more of their body weight and had higher (worse) performance status. Patients reporting more than 1 symptom also had lower LCS scores. Change in LCS scores over 12 weeks was associated with time to disease progression and response to treatment, with patients showing a complete or partial response (CR/PR) having more positive changes than patients showing progressive disease. In these analyses, a change of 2–3 points on the LCS was determined to be a clinically meaningful difference.

### Symptom Assessment in Lung Cancer

Lung cancer is a disease of symptoms, ranging from mild to debilitating.<sup>84-86</sup> The most common symptoms reported by patients with lung cancer are fatigue, dyspnea, cough, pain, weight loss, and change in mental status.<sup>87</sup> Clinical care frequently involves careful monitoring of the tradeoffs between symptom relief and treatment-related side effects.

### Development of Disease-Specific Symptom Indices

Some of the most widely used multidimensional HRQL instruments, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30<sup>88</sup> and the FACT-general,<sup>89</sup> include a few common cancer symptoms such as pain, fatigue and nausea, and can be aggregated to produce a total HRQL score. One limitation to the use of global HRQL scores to measure symptom status is that they may obscure important and significant changes in disease-related symptoms.<sup>90</sup> The nesting of tumor-specific symptoms within these larger multidimensional questionnaires, however, creates an opportunity to derive targeted symptom scales that are disease-specific, precise, and clinically appropriate, as advocated by the clinical and regulatory communities.<sup>91</sup>

One example of an effort to create psychometrically sound symptom-focused measures is the authors' recent collaboration with the National Comprehensive Cancer Network (NCCN), an alliance of cancer centers across the United States. The purpose of this collaboration was to derive 9 tumor-specific indices of the most important symptoms and concerns to evaluate treatment for advanced bladder, brain, breast, colorectal, head and neck, hepatobiliary/pancreas, lung, ovarian, and prostate cancers.<sup>76</sup> Nine tumor-specific symptom indices were constructed with the input of 223 physicians and 232 nurses at 17 NCCN member institutions. Symptom questions were extracted from the FACT measurement system. The resulting NCCN/FACT symptom indices are comprised of 6–15 items, depending on disease. Acquisition of patient input into the selection of priority symptoms for treatment in advanced cancer is a logical next step and is underway, along with validation of these indices in patient populations.

### Psychological Distress and Neuropsychiatric Symptoms

In addition to somatic symptoms, some studies have also documented the psychological distress and neuropsychiatric symptoms experienced by some patients during treatment

for advanced lung cancer. To examine the trajectory of these symptoms during treatment for NSCLC and extensive SCLC, HRQL data collected from 2 ECOG clinical trials (E5592 and E7593) were analyzed.<sup>92</sup> Patients enrolled in E5592 completed the FACT-L at randomization and at weeks 6 and 12 and 6 months, and patients enrolled in E7593 completed the FACT-L at randomization (following 4 cycles of cisplatin plus etoposide) and at weeks 6 and 15. Clinical significance was determined by calculating the proportion of patients who reported symptom frequency as “quite a bit” or “very much” at each assessment. Approximately 20% of patients reported experiencing clinically significant psychological distress and neuropsychiatric symptoms at randomization or during treatment. This percentage is likely to be an underestimation of the general lung cancer population because these trials only admitted patients with performance status of 0 or 1, and because of the association between patient withdrawal and toxicity and disease progression. While the proportion of patients with clinically significant fatigue, appetite loss, and treatment side-effect bother increased over the course of the trials, 3 symptoms declined in prevalence: pain, general worry, and worry about dying. The results underscore the importance of assessing and treating psychological distress and neuropsychiatric symptoms as a standard part of clinical management.

### From Clinical Trials to Clinical Practice

More recently, studies have demonstrated the feasibility and acceptability of using HRQL and symptom information as routine components of care in daily clinical practice.<sup>93-96</sup> In each of these studies, computer technology was used to facilitate assessment administration, presentation of data and interpretation of the results. Despite the increased recognition of the importance of HRQL, routine assessment and integration of HRQL information into the clinical setting has not yet occurred.

### Barriers to Assessing HRQL Data in Clinical Practice

In a review of the literature, Davis and Cella<sup>97</sup> identified 3 broad categories of barriers to routine assessment of HRQL in the clinical setting. These include: (1) provider inexperience with formal HRQL assessments, (2) methodological concerns, and (3) logistic barriers that constrain the feasibility of clinical implementation and integration. Provider inexperience includes lack of familiarity with available instruments and lack of knowledge about the potential usefulness of HRQL information to enhance patient-physician communication.<sup>93,95,98-100</sup> Methodological concerns stem from real or perceived lack of psychometric robustness in some measures, including the ability to detect clinically meaningful change and the inability to compare scores across time and across instruments.<sup>98,101,102</sup> Finally, logistic barriers include burden on patient and staff associated with HRQL assessment and the unavailability of results in real-time during the clinical encounter.<sup>99-101,103</sup> Regardless of the potential utility of HRQL data in the clinical management of patients with lung cancer, these barriers represent significant challenges to the incorporation of routine assessment of HRQL as a standard

component of patient care. Efforts are currently underway to address some of these barriers in an attempt to advance the use of HRQL assessments in routine clinical care. These efforts will be described below.

### Clinical Applications of HRQL Assessment

In a study of patients with advanced NSCLC,<sup>101</sup> physicians used HRQL data collected at 4 different physician visits (baseline, weeks 6 and 12, and 6 months) to guide treatment decisions. At baseline, patients completed demographic and health history questionnaires and a handheld computer-based version of the FACT-L<sup>42</sup> followed by an evaluation of the computerized assessment. Oncologists were presented with FACT-L data for each patient, including 4 subscale scores (PWB, social/family well-being, emotional well-being, FWB), LCS, TOI, and a total score. Oncologists reviewed individual results prior to each consult, allowing them to discuss the HRQL results with each patient. Feedback from oncologists included recommendations for more frequent HRQL assessments to capture the variability of patients' HRQL and the availability of results in real-time.<sup>101</sup>

The physician feedback led to the development of an ongoing pilot study that involves weekly symptom monitoring for patients with advanced NSCLC or SCLC beginning any line of treatment. Patients call into a computerized telephone survey system to complete a 14-item symptom index weekly for 12 weeks. The symptom index assesses common lung cancer symptoms such as fatigue, pain, shortness of breath, nausea, decreased appetite, dyspnea, emotional distress, treatment side-effect bother, and overall HRQL. The system is monitored daily by a nurse, who contacts any patient reporting the presence or sustained high level of a symptom ("symptom alert"). The patient and his/her oncologist are then called to discuss the identified symptom(s) and determine a plan of action. Cumulative graphic summary reports are generated, reviewed, and discussed with patients at each physician visit. Additionally, both patients and oncologists rate the acceptability and satisfaction with the symptom monitoring program and the understandability of the summary report. To date, patient compliance with the symptom monitoring has been high (92%), and both patient and physician acceptance has been very favorable. Seventy-one percent of patients had at least 1 symptom alert during the 12-week study period, with the most commonly reported symptoms being treatment side effect bother, pain, dyspnea, discontent with HRQL, cognitive dysfunction, and nausea.<sup>104</sup>

### Conclusion

Lung cancer, an increasingly prevalent disease with poor prognosis, is associated with a variety of physical and neuropsychiatric symptoms as well as generally poor HRQL. As lung cancer often goes undetected until it progresses to an advanced stage, treatment tends to be palliative with a focus on symptom management rather than cure. While standard treatment regimens have proven to be quite toxic, the newer therapies have demonstrated less toxic side effect profiles, offering patients the potential for extending the quality as well

as the quantity of life. As HRQL data is being more routinely collected in RCTs the ability to examine the relationship between HRQL and the more traditional clinical endpoints has become more feasible. To date, the large amount of missing HRQL data due to patient, treatment, and disease-related factors poses the most significant limitation in the interpretation of HRQL results. Yet, several investigators have suggested strategies to handle the problem of missing data. Increasingly, efforts are being directed toward the incorporation of HRQL data into routine clinical practice. It is hoped that the regular use of HRQL data will enhance clinical care through standard means for early detection of problems and symptom management. Ultimately, it is believed that such improvements will translate into improved patient-provider communication and patient satisfaction.

### References

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer*. 1999;80:827-841.
2. American Cancer Society. Cancer Facts and Figures 2002. Atlanta, Ga.
3. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer Statistics, 2001. *CA Cancer J Clin*. 2001;51:15-36.
4. American Cancer Society. Cancer Facts and Figures 2003. Atlanta, Ga.
5. American Thoracic Society/European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. *Am J Respir Crit Care Med*. 1997;156:320-332.
6. Ries KA, Miller BA, Hankey BF, Kosay CL, HARRAS A, Edwards BK, eds. Lung and bronchus. In: *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*. Bethesda, Md: National Cancer Institute; NIH Pub. No 94-2789; 1994:263-286.
7. Travis W, Linder J, Mackay B. Classification, histology, cytology, and electron microscopy. In: Pass HI, Mitchell JB, Johnston DH, et al, eds. *Lung Cancer, Principles and Practice* 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000:453-495.
8. Feld R, Sagman U, LeBlanc M. Staging and prognostic factors for small cell lung cancer. In Pass HI, Mitchell JB, Johnston DH, et al. (eds.) *Lung Cancer, Principles and Practice*. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000:612-627.
9. Jacobsen PB, Weitzner MA. Evaluation of palliative endpoints in oncology clinical trials. *Cancer Control*. 1999;6:471-477.
10. McVie JG. Non-small lung cancer: meta-analysis of efficacy of chemotherapy. *Semin Oncol*. 1996;23(3 suppl 7):12-14.
11. Moynour CM. Measuring quality of life: an emerging science. *Semin Oncol*. 1994;21(suppl):48-60.
12. Splinter TA. Chemotherapy in advanced non-small lung cancer. *Eur J Cancer*. 1990; 26:1093-1099.
13. Fergusson RJ, Cull A. Quality of life measurement for patients undergoing treatment for lung cancer. *Thorax*. 1991;46:671-675.
14. Kaasa S, Mastekaasa A, Thorud E. Toxicity, physical function and everyday activity reported by patients with inoperable non-small cell lung cancer in a randomized trial (chemotherapy versus radiotherapy). *Acta Oncol*. 1988;27:343-349.
15. Cella DF, Orofiamma B, Holland JC, et al. The relationship of psychological distress, extent of disease, and performance status in patients with lung cancer. *Cancer*. 1987;60:1661-1667.
16. Sarna L. Functional status in women with lung cancer. *Cancer Nurs*. 1994;17:87-93.
17. Mountain CF. Assessment of the role of surgery for control of lung cancer. *Ann Thorac Surg*. 1977;24:365-373.
18. McCormack PM, Bains MS, Martini N, et al. Methods of skeletal reconstruction following resection of lung cancer invading the chest wall. *Surg Clin North Am*. 1987;67:979-986.
19. Holmes E, Gail M. Surgical adjuvant therapy for stage II and stage III adenocarcinoma and large-cell undifferentiated carcinoma. *J Clin Oncol*. 1986;4:710-715.

20. The Lung Cancer Study Group. The benefit of adjuvant treatment for resected locally advanced non-small-cell lung cancer. *J Clin Oncol.* 1988;6:9-17.
21. Niiranen A, Niitamo-Korhonen S, Kouri M, et al. Adjuvant chemotherapy after radical surgery for non-small cell lung cancer: a randomized study. *J Clin Oncol.* 1992;10:1927-1932.
22. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ.* 1995;311:899-909.
23. Faber LP, Kittle CF, Warren WH, et al. Preoperative chemotherapy and irradiation for stage III non-small cell lung cancer. *Ann Thorac Surg.* 1989;47:669-675.
24. Skarin A, Jochelson M, Sheldon T, et al. Neoadjuvant chemotherapy in marginally resectable stage III M0 non-small cell lung cancer: long-term follow-up in 41 patients. *J Surg Oncol.* 1989;40:266-274.
25. Weiden P, Piantadosi S. Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small-cell lung cancer: a phase II study of the Lung Cancer Study Group. *J Natl Cancer Inst.* 1991;83:266-273.
26. Burkes RL, Ginsberg RJ, Shepard FA, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small-cell lung cancer: results of the Toronto Phase II Trial. *J Clin Oncol.* 1992;10:580-586.
27. Strauss GM, Herndon JE, Sherman DD, et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: report of a Cancer and Leukemia Group B phase II study. *J Clin Oncol.* 1992;10:1237-1244.
28. Martini N, Kris MG, Flehinger BJ, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. *Ann Thorac Surg.* 1993;55:1365-1374.
29. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med.* 1994;330:153-158.
30. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst.* 1994;86:673-680.
31. de Boer RH, Smith IE, Pastorino U, et al. Pre-operative chemotherapy in early stage resectable non-small-cell lung cancer: a randomized feasibility study justifying a multicenter phase III trial. *Br J Cancer.* 1999;79:1514-1518.
32. Carney D, Shepard F. *Treatment of small cell lung cancer: Chemotherapy.* In: Hansen HH (ed): The International Association for the Study of Lung Cancer Textbook of Lung Cancer. London: Martin Dunitz Publishers; 2000:26-272.
33. Shepard FA. The role of chemotherapy in treatment of small cell lung cancer [review]. *Chest Surg Clin N Am.* 1997;7:113-133.
34. Jacoulet P, Depierre A, Moro D, et al. Long-term survivors of small-cell lung cancer (SCLC): a French multicenter study. Groupe d'Oncologie de Langue Francaise. *Ann Oncol.* 1997;8:1009-1014.
35. Steele JP. Gemcitabine/carboplatin versus cisplatin/etoposide for patients with poor-prognosis small cell lung cancer: a phase III randomized trial with quality-of-life evaluation. *Semin Oncol.* 2001;28(3 suppl 10):15-18.
36. Kotalik J, Yu E, Markman BR, et al. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2001;50:309-316.
37. Qian W, Parmar MK, Sambrook RJ, Fayers PM, Girling DJ, Stephens RJ. Analysis of messy longitudinal data from a randomized clinical trial. MRC Lung Cancer Working Party. *Stat Med.* 2000;19:2657-2674.
38. Hollen PJ, Gralla RJ, Cox C, Eberly SW, Kris MG. A dilemma in analysis: issues in the serial measurement of quality of life in patients with advanced lung cancer. *Lung Cancer.* 1997;18:119-136.
39. Herndon JE 2nd, Fleishman S, Kosty MP, Green MR. A longitudinal study of quality of life in advanced non-small cell lung cancer: Cancer and Leukemia Group B (CALGB) 8931. *Control Clin Trials.* 1997;18:286-300.
40. Fairclough DL. Design and analysis of quality of life studies in clinical trials. Boca Raton, Fla: Chapman & Hall/CRC; 2002:69-91.
41. Olschewski M, Schulgen G, Schumacher M, Altman DG. Quality of life assessment in clinical cancer research. *Br J Cancer.* 1994;70:1-5.
42. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer.* 1995;12:199-220.
43. Bottomley A, Efficace F, Thomas R, Vanvoorden V, Ahmedzai SH. Health-related quality of life in non-small-cell lung cancer: methodologic issues in randomized controlled trials. *J Clin Oncol.* 2003;21:2982-2992.
44. Montazeri A, Gillis CR, McEwen J. Quality of life in patients with lung cancer: a review of literature from 1970 to 1995. *Chest.* 1998;113:467-481.
45. Hopwood P, Stephens RJ, Machin D. Approaches to the analysis of quality of life data: experiences gained from a Medical Research Council Lung Cancer Working Party palliative chemotherapy trial. *Qual Life Res.* 1994;3:339-352.
46. Zee BC. Growth curve model analysis for quality of life data. *Stat Med.* 1998;17:757-766.
47. Hahn EA, Webster KA, Cella D, Fairclough DL. Missing data in quality of life research in Eastern Cooperative Oncology Group (ECOG) clinical trials: problems and solutions. *Stat Med.* 1998;17:547-559.
48. Fairclough DL, Peterson HF, Cella D, Bonomi P. Comparison of several model-based methods for analysing incomplete quality of life data in cancer clinical trials. *Stat Med.* 1998;17:781-796.
49. Hollen PJ, Gralla RJ, Kris MG, Eberly SW, Cox C. Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). *Support Care Cancer.* 1999;7:140-148.
50. Chute CG, Greenberg ER, Baron J, Korson R, Baker J, Yates J. Presenting conditions of 1539 population-based lung cancer patients by cell type and stage in New Hampshire and Vermont. *Cancer.* 1985;56:2107-2111.
51. Grilli R, Oxman AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? *J Clin Oncol.* 1993;11:1866-1872.
52. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet.* 1993;342:19-21.
53. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F. Chemotherapy vs. supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest.* 1994;106:861-865.
54. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst.* 1999;91:66-72.
55. Ganz PA, Figlin RA, Haskell CM, La Soto N, Siau J. Supportive care versus supportive care and combination chemotherapy in metastatic non-small cell lung cancer. Does chemotherapy make a difference? *Cancer.* 1989;63:1271-1278.
56. Helsing M, Bergman B, Thaning L, Hero U. Quality of life and survival in patients with advanced non-small cell lung cancer receiving supportive care plus chemotherapy with carboplatin and etoposide or supportive care only. A multicentre randomised phase III trial. Joint Lung Cancer Study Group. *Eur J Cancer.* 1998;34:1036-1044.
57. Thongpassert S, Sanguanmitra P, Juthapan W, et al. Relation between quality of life and clinical outcomes in advanced non-small cell lung cancer: best supportive care (BSC) plus chemotherapy. *Lung Cancer.* 1999;24:17-24.
58. Anderson H, Hopwood P, Stephens RJ, et al. Gemcitabine plus best supportive care (BSC) vs. BSC in inoperable non-small cell lung cancer: a randomized trial with quality of life as the primary outcome. *Br J Cancer.* 2000;83:447-453.
59. Ranson M, Davidson N, Nicolson M, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. *J Nat Cancer Inst.* 2000;92:1074-1080.
60. Roszkowski K, Pluzanska A, Krzakowski M, et al. A multicenter, randomized, phase III study of docetaxel plus supportive care versus best supportive care in chemotherapy-naïve patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer.* 2000;27:145-57.
61. Shepard F, Dancey J, Ramlau R, et al. Prospective randomized trial of

- docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18:2095-2103.
62. Bunn PA Jr, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res*. 1998;4:1087-1100.
  63. Fossella FV, Devore R, Kerr RN, et al. Randomized Phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000;18:2354-2360.
  64. Socinski M, Schell M, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small cell lung cancer. *J Clin Oncol*. 2002;20:1335-1343.
  65. Dancey J, Shepherd F, Ramlau R, et al. Quality of life (QoL) assessment in randomized study of taxotere (TAX) versus best supportive care (BSC) in non-small cell lung cancer (NSCLC) patients (pts) previously treated with platinum-based chemotherapy [abstract]. *Proc Am Soc Clin Oncol*. 1999;18:491a.
  66. Plunkett T, Chrystal K, Harper P. Quality of life and the treatment of advanced lung cancer. *Clin Lung Cancer*. 2003;5:28-32.
  67. Thatcher N, Girling D, Hopwood P, et al. Improving survival without reducing quality of life in small-cell-lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor-support: results of a British Medical Research Council multicenter randomized trial. Medical Research Council Lung Cancer Working Party. *J Clin Oncol*. 2000;18:395-404.
  68. Wolf M, Pritsch M, Drings P, et al. Standard vs. palliation chemotherapy in metastatic small cell lung cancer: an analysis on treatment efficacy and quality of life. *Lung Cancer*. 1994;11:s92.
  69. Gower NH, Rudd RM, Ruiz de Elvira MC, et al. Assessment of quality of life using daily diary card in a randomised trial of chemotherapy in small-cell lung cancer. *Ann Oncol*. 1995;6:575-580.
  70. Bleehen NM, Fayers PM, Girling DJ, et al. Controlled trial of 12 versus six courses of chemotherapy in the treatment of small-cell lung cancer. *Br J Cancer*. 1989;59:584-590.
  71. Geddes D M, Dones L, Hill E, et al. Quality of life during chemotherapy for small cell lung cancer: assessment and use of daily diary card in a randomised trial. *Eur J Cancer*. 1990;26:484-492.
  72. Rowinsky E. EGFR-targeted cancer therapies: Is there a need to reconsider clinical trial design? A discussion of how, and why clinical trial design should be altered for the clinical evaluation of EGRF-targeted therapies. *Signal*. 2001;2:4-12.
  73. Douillard J-Y, Giaccone G, Horai T, et al. Improvement in disease related symptoms and quality of life in patients with advanced non-small cell lung cancer (NSCLC) treated with ZD1839 ('Iressa') (IDEAL) [abstract]. *Proc Am Soc Clin Oncol*. 2002;21:299a. Abstract 1195.
  74. Kris M, Natale R, Herbst R, et al. Efficacy of Gefitinib, an inhibitor of the epidermal growth factor receptor Tyrosine Kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial (IDEAL 2). *JAMA*. 2003;290:2149-2158.
  75. Natale R, Skarin A, Maddox A-M, et al. Improvement in symptoms and quality of life for advanced non-small cell lung cancer patients receiving ZD1839 ('Iressa') in (IDEAL 2) [abstract]. *Proc Am Soc Clin Oncol*. 2002;21:292a. Abstract 1167.
  76. Cella D. Impact of ZD 1839 on non-small cell lung cancer-related symptoms as measured by the Functional Assessment of Cancer Therapy-Lung-Scale. *Semin Oncol*. 2003;30:39-38.
  77. Ganz P, Lee J, Siau J. Quality of life assessment: an independent prognostic variable for survival in lung cancer. *Cancer*. 1991;67:3131-3135.
  78. Cella D, Webster K. Linking outcomes management to quality of life measurement. *Oncology (Huntington)*. 1997;11:232-235.
  79. Buccheri GF, Ferrigno D, Tamburini M, et al. The patient's perception of his own quality of life might have an adjunctive prognostic significance in lung cancer. *Lung Cancer*. 1995;12:45-58.
  80. Montazeri A, Milroy R, Hole D, et al. Quality of life in lung cancer patients: an important prognostic factor. *Lung Cancer*. 2001;31:233-240.
  81. Eton D, Fairclough D, Cella D, et al. Early changes in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: results from Eastern Cooperative Oncology Group Study 5592. *J Clin Oncol*. 2003;21:1536-1543.
  82. McCorkle R. Development of a symptom distress scale. *Cancer Nurs*. 1978;1:373-378.
  83. Kukul WA, McCorkle R, Driever M. Symptom distress, psychosocial variables and lung cancer survival. *J Psychosoc Oncol*. 1986;4:91-104.
  84. Earle CC, Evans WK. Management issues for stage IV non-small-cell lung cancer. *Cancer Control*. 4:307-316.
  85. Hollen P, Gralla R, Kris M, et al. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). *Eur J Lung Cancer*. 1993;29A (suppl 1):S51-S58.
  86. Soni M, Cella D, Masters G, et al. The validity and clinical utility of symptom monitoring in advanced lung cancer: a literature review. *Clin Lung Cancer*. 2002;4:1-8.
  87. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. *J Pain Symptom Manage*. 2000;19:137-53.
  88. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a Quality-of-Life Instrument for use in international clinical trials in oncology. *J Nat Cancer Inst*. 1993;85:365-376.
  89. Cella DF. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570-579.
  90. Food and Drug Administration Oncologic Drugs Advisory Committee (ODAC) Quality Of Life Subcommittee Meeting Transcript, February 10, 2000.
  91. Geels P, Eisenhauer E, Bezjak A, et al. Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. *J Clin Oncol*. 2000;18:2395-2405.
  92. Wagner LI, Rue M, Fisch M, et al. Neuropsychiatric symptoms during cancer treatment: an examination of quality of life data from two ECOG lung cancer trials [abstract]. *Proc Am Soc Clin Oncol*. 2002;21:357a.
  93. Carlson L, Specia M, Hagen N, et al. Computerized quality of life screening in a cancer pain clinic. *J Palliative Care*. 2001;17:46-52.
  94. Taenzler P, Bultz B, Carlson L, et al. Impact of computerized quality of life screening on physician behavior and patient satisfaction in lung cancer outpatients. *Psycho-Oncology*. 2000;9:203-213.
  95. Velikova G, Brown J, Smith A, et al. Computer-based quality of life questionnaires may contribute to doctor patient interactions in oncology. *Br J Cancer*. 2002;86:51-59.
  96. Velikova G, Brown J, Booth L, et al. A randomized study of quality of life measurements in oncology practice-effects on patient well-being and process of care. *Proc Am Soc Clin Oncol*. 2003;22:728.
  97. Davis K, Cella D. Assessing quality of life in oncology clinical practice: a review of barriers and critical success factors. *J Clin Outcomes Manage*. 2002;9:327-332.
  98. Bezjak A, Ng P, Skeel R, et al. Oncologists' use of quality of life information: results of a survey of Eastern Cooperative Oncology Group Physicians. *Quality of Life Research*. 2001;10:1-13.
  99. Velikova G, Wright P, Smith AB, et al. Self-reported quality of life of individual cancer patients: concordance of results with disease course and medical records. *J Clin Oncol*. 2001;19:2064-2073.
  100. Morris J, Perez D, McNoe B. The use of quality of life data in clinical practice. *Qual Life Res*. 1998;7:85-91.
  101. Chang C-H, Cella D, Masters G, et al. Real-time clinical application of quality of life assessment in lung cancer. *Clin Lung Cancer*. 2002;4:104-109.
  102. Chang C, Cella D. Equating health-related quality of life instruments in applied oncology settings. *Physical Medicine and Rehabilitation: States of the Art Reviews*. 1997;11:397-406.
  103. Detmar S, Aaronson N. Quality of life assessment in daily clinical oncology practice: a feasibility study. *Eur J Cancer*. 1998;34:1181-1186.
  104. Yount S, Davis K, Khan S, et al. Real-time symptom monitoring of patients with advanced lung cancer [abstract]. *Quality of Life Research*. 2003;12:725. Abstract 1632.